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Sleep in seasonal affective disorder patients in forced desynchrony: an explorative study

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SUMMARY The majority of winter-type seasonal affective disorder (SAD) patients complain of hypersomnia and daytime drowsiness. As human sleep is regulated by the interaction of circadian, ultradian and homeostatic processes, sleep disturbances may be caused by either one of these factors. The present study focuses on homeostatic and ultradian aspects of sleep regulation in SAD. Sleep was recorded polysomnographically in seven SAD patients and matched controls subjected to a 120-h forced desynchrony protocol. In time isolation, subjects were exposed to six 20-h days, each comprising a 6.5-h period for sleep. Patients participated while being depressed, while remitted after light therapy and in summer. Controls were studied in winter and in summer. In each condition, the data of each subject were averaged across all recordings. Thus, the influence of the effects of the circadian pacemaker on sleep was excluded mathematically. The comparison of patients with controls and with themselves in the various conditions revealed no abnormalities in homeostatic parameters: sleep stage variables, relative power spectra and time courses of power in various frequency bands across the first three non-rapid eye movement–rapid eye movement (NREM–REM) cycles showed no differences. The data suggest that homeostatic processes are not involved in the disturbance of sleep in SAD.

KEYWORDS circadian pacemaker, forced desynchrony, process C, process S, seasonal affective disorder, sleep regulation

INTRODUCTION

Most seasonal affective disorder (SAD) patients complain of hypersomnia and daytime drowsiness (Anderson *et al.* 1994; Rosenthal *et al.* 1984). This suggests that in SAD sleep regulation may be altered. Because of the seasonal recurrence of symptoms and the efficacy of light therapy the pathogenesis of SAD is thought to be linked to disturbances of the circadian pacemaker. The potential depressogenic role of dysregulation of sleep is relatively seldom addressed. Homeostatic, ultradian, and circadian pacemaker related mechanisms are all involved in the regulation of sleep (Borbely 1982; Daan *et al.* 1984; Dijk and Czeisler 1994, 1995; Wyatt *et al.* 1999). Therefore, the subjective and objective sleep abnormalities in SAD might be

caused by disturbances of either circadian or non-circadian components of sleep regulation. The present study is devoted to the exploration of the homeostatic and ultradian aspects of sleep regulation in SAD.

According to the generally accepted two-process model of sleep, the alternation of wakefulness and sleep is regulated by an interaction of a circadian pacemaker related process 'C' and a homeostatic, or sleep–wake cycle related process 'S' (Borbely 1982; Daan *et al.* 1984). Additionally, Dijk and Czeisler (1994) have postulated that the interaction of the circadian pacemaker and the sleep–wake cycle promotes wakefulness during the day and facilitates sleep during the night. The human circadian pacemaker, localized in the suprachiasmatic nuclei (SCN) of the brain, generates near-24-h oscillations in many physiological and psychological processes (Aschoff 1965; Czeisler *et al.* 1999). By its sensitivity to light, the circadian pacemaker synchronizes these oscillatory processes with the 24-h environmental light–dark cycle. (Boivin *et al.* 1996; Honma and

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Honma 1988; Jewett *et al.* 1997; Minors *et al.* 1991). However, overt circadian rhythms measured under normal conditions comprise a mixture of both pacemaker related and sleep–wake cycle related contributions. Forced desynchrony protocols have been designed to distinguish the influences of the circadian pacemaker from those of the sleep–wake cycle (Czeisler *et al.* 1986; Dijk *et al.* 1992; Hiddinga *et al.* 1997; Kleitman and Kleitman 1953). Forced desynchrony studies have demonstrated circadian- and sleep-dependent components in the distribution of non-rapid eye movement sleep (NREMs), slow wave sleep (SWS), spindle activity, and the latency to the first episode of rapid eye movement (REM) sleep (Dijk and Czeisler 1995; Wyatt *et al.* 1999). In other words, the polysomnographically recorded sleep data obtained in forced desynchrony studies in healthy subjects have shown that sleep is regulated by the interaction of circadian and homeostatic influences (Dijk and Czeisler 1994, 1995; Wyatt *et al.* 1999).

Sleep abnormalities are a prominent feature of mood disorders (Benca *et al.* 1992). Most non-seasonally depressed patients complain of insomnia (i.e. difficulties falling asleep, increased wakefulness during the sleeping period, early morning awakening) and do not feel restored after sleep (Benca *et al.* 1997). Compared with those obtained in healthy controls, polysomnographic recordings in affective disorder patients have consistently revealed a decreased sleep continuity, a reduction in SWS, a shortening of the REM sleep latency (SL) and an increase of REM sleep in the first part of the night (reviewed in Benca *et al.* 1992). In contrast, about 80% of the SAD patients suffer from hypersomnia with earlier sleep onset and later wake times (Anderson *et al.* 1994). In several studies polysomnographically recorded sleep in SAD has been examined. Recordings of SAD patients in winter were compared with those in summer (Anderson *et al.* 1994; Endo *et al.* 1992; Palchikov *et al.* 1997; Rosenthal *et al.* 1984, 1985, 1989) and with those in control subjects in winter (Anderson *et al.* 1994; Rosenthal *et al.* 1989; Schwartz *et al.* 2000). Furthermore, comparisons have been made between recordings of SAD patients in winter before and after light treatment (Anderson *et al.* 1994; Brunner *et al.* 1996; Endo 1993; Kohsaka *et al.* 1994; Palchikov *et al.* 1997; Partonen *et al.* 1993; Rosenthal *et al.* 1989). Sleep in SAD patients in winter was found to differ from sleep in matched controls, but the sleep pattern which is characteristic for non-seasonal depression has not been observed. One study of polysomnographic recordings of seasonal and non-seasonal affective disorder revealed that seasonality is not characterized by a particular pattern of electroencephalogram (EEG) characteristics (Thase 1989). Furthermore, it was shown that light therapy or the change of season can correct some of the polysomnographic abnormalities observed in SAD, although in one study no such changes were found (Partonen *et al.* 1993). Finally, a study should be mentioned in which baseline sleep and sleep following the total sleep deprivation of a 40-h constant routine protocol were recorded in SAD patients and controls. The patients exhibited a normal homeostatic regulation of sleep (Brunner *et al.* 1996). In contrast, the analysis of EEG theta–

alpha activity of SAD patients and controls during the waking hours of a 40-h constant routine procedure in both winter and summer suggested that SAD patients may have a trait deficiency of process S, as expressed by a deficient buildup of sleep pressure during extended wakefulness (Cajochen *et al.* 2000).

The polysomnographic changes found in depression and the pronounced but temporary effects of sleep deprivation on depressive symptomatology led to hypotheses concerning the involvement of either process C (e.g. an abnormality of circadian phase relative to the timing of the sleep–wake cycle, or a blunted circadian amplitude), or process S (a deficiency in the homeostatic buildup of sleep pressure), or both in the pathogenesis of affective disorders (reviewed in for example Boivin 2000; Wirz-Justice 1995; Wirz-Justice and Van den Hoofdakker 1999). The seasonality of symptoms and the efficacy of light therapy have especially favored hypotheses concerning the involvement of circadian pacemaker abnormalities in SAD. This led to the present forced desynchrony study in SAD patients and matched controls. In a previous analysis of core body temperature and melatonin obtained in the same protocol some characteristics of process C were examined. No differences were observed between SAD patients and controls with respect to the period and phase position of the circadian pacemaker (Koorengevel *et al.* 2002). The aim of the present analysis is to examine process S. During the forced desynchrony protocol sleep was scheduled at all circadian phases. Thus, by averaging the sleep data, the impact of circadian phase could be minimized, if not excluded completely. Additionally, to avoid differences between patients and controls due to differences in habitual sleep timing, subjects were instructed to sleep between midnight and 8 AM during four baseline days at home as well as subjected to a habituation night in the lab prior to the start of the experiment.

METHODS

Recruitment and selection criteria

SAD patients who in previous years responded favorably to morning bright light therapy were recruited from the out-patients clinic. Healthy control subjects who could be matched to one of the participating patients for age, sex, smoking habits and menstrual cycle phase (if appropriate) were approached through local newspaper and television advertisements. All subjects received written information about the study. Before entering the protocol, the study was explained verbally to the subjects. Thereafter, subjects gave written informed consent. The study was approved by the Medical Ethics Committee of the Groningen Academic Hospital. Subjects were paid for their participation.

Patients fulfilled the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria for recurrent major depression with seasonal pattern (American Psychiatric Association 1994) and the Rosenthal criteria for SAD

(Rosenthal *et al.* 1984). Controls reported no psychopathological disturbances or sleeping problems. Before inclusion in the study, subjects rated their general mental health, depressive symptomatology, seasonality and the preference for morningness or eveningness by completing the following questionnaires: (1) the General Health Questionnaire (GHQ; Goldberg and Williams 1988), (2) the Beck Depression Inventory (BDI; Beck *et al.* 1979) and the Structured Interview Guide for the Hamilton Rating Scale of Depression – self-rating version (SIGH-SAD-SR; Williams *et al.* 1992), (3) the Seasonal Pattern Assessment Questionnaire (SPAQ; Rosenthal *et al.* 1987), and (4) the Morningness–Eveningness questionnaire (M–E; Horne and Ostberg 1976). The SIGH-SAD-SR consists of the 21-item Hamilton Rating Scale for Depression (HRSD) and an 8-item atypical scale (ATYP) addressing atypical symptoms such as an increase in sleep. An M–E score below 30 and above 70 reflects eveningness and morningness, respectively (Horne and Ostberg 1976). Controls required a score of below 3 on the GHQ, below 9 on the BDI and below 8 on the SIGH-SAD-SR as well as on the SPAQ (Kasper *et al.* 1989).

Subjects were physically fit, not dependent on alcohol or other substances and medication-free at least 1 month prior to participation (with the exception of the sporadic use of NSAIDs). Patients had not used psychoactive medications during at least 6 months before entering the study. Menstrual cycle phase was assessed through self-report. If appropriate, the use of oral contraceptives, a depot progesterone or estrogen-replacement therapy was continued.

During the winter season, depressive symptoms were monitored in patients by means of weekly BDI and SIGH-SAD-SR ratings. Patients were invited for participation during a depressive episode ($BDI \geq 16$), when remitted after light therapy ($BDI < 6$) and in summer. After finishing the protocol during the depressive episode, 45 min of 10 000 lux morning light therapy was administered at the out-patients clinic for at least five consecutive days. Controls participated once in winter and once in summer.

Subjects

From 1997 until 1999, the winter and summer experiments were scheduled during the months of October–March and May–August, respectively. Seven SAD patients (one male and six females) and eight matched controls (one male and seven females) participated. Baseline scores on the GHQ, SPAQ and the M/E and the scores on the SIGH-SAD-SR and BDI completed on day 1 of the protocol are summarized in Table 1. For the SIGH-SAD-SR, the HRSD and ATYP scores are listed separately. Furthermore, for each condition the score on the hypersomnia item of the SIGH-SAD-SR is presented. During the depressive episode, six of seven patients reported to sleep at least 1 h more than when not depressed. A repeated measures analysis of variance (ANOVA) of hypersomnia scores, with season as repeated measures factor and patient/control status as between subjects factor, revealed a significant effect of season and of patient/control status and a significant interaction effect if patients were included in winter in their depressed state ($F > 7.26$, $P < 0.02$). Significance disappeared if patients in winter were studied in the remitted state ($F < 1.68$, $P > 0.22$). Apparently, during the depressive episode, SAD patients were more hypersomnic than in the other conditions and than controls. After participating in summer, one female control subject cancelled the second experiment and was therefore replaced by another matched control for the winter condition. In both groups, three subjects were cigarette smokers. Of the female patients, four were studied each time in the (pseudo-) follicular phase of their menstrual cycle and one in the pseudo-luteal phase. ('pseudo' is referring to situations induced by oral contraceptives). The female controls were matched for menstrual cycle phase, except for one control matched to a postmenopausal patient who participated in the pseudo-luteal phase while depressed and in the pseudo-follicular phase while remitted as a result of estrogen replacement therapy.

Table 1 Characteristics (mean \pm SD) of subjects: age at times of first participation, scores on the General Health Questionnaire (GHQ), Seasonal Pattern Assessment Questionnaire (SPAQ), and Morningness–Eveningness Questionnaire (M–E) which were completed at baseline and scores on the Beck Depression Inventory (BDI), on the Structured Interview Guide for the Hamilton Rating Scale of Depression – self-rating version (SIGH-SAD-SR) at day 1 of the protocol. The SIGH-SAD-SR subscores on the Hamilton Rating Scale of Depression (HRSD), the atypical symptom list (ATYP) and SIGH-SAD-SR item 14 on complaints of hypersomnia are listed separately. Seasonal affective disorder (SAD) patients participated during a depressive episode, remitted after light therapy and in summer. Controls participated once in winter and once in summer

	SAD patients ($n = 7$)			Controls ($n = 7$)	
	Depressed	Remitted	Summer	Winter	Summer
Age	36.3 \pm 13.9			38.1 \pm 12.8	
GHQ	1.4 \pm 2.3			0.3 \pm 0.5	
SPAQ	16.7 \pm 3.6			3.5 \pm 1.8	
M–E	44.7 \pm 10.4			51.4 \pm 13.7	
BDI	20.3 \pm 6.1	1.7 \pm 1.8	0.6 \pm 0.8	0.3 \pm 0.8	0.3 \pm 0.5
SIGH-SAD-SR	32.3 \pm 11.8	3.7 \pm 4.3	1.1 \pm 1.9	1.4 \pm 2.1	1.6 \pm 1.6
HRSD	21.3 \pm 7.9	2.0 \pm 2.2	0.9 \pm 1.5	0.9 \pm 0.9	1.3 \pm 1.5
ATYP	11.0 \pm 5.4	1.7 \pm 2.2	0.3 \pm 0.5	0.6 \pm 1.5	0.3 \pm 0.8
Hypersomnia (item 14)	2.0 \pm 1.3	0.3 \pm 0.5	0.3 \pm 0.5	0.1 \pm 0.4	0.0 \pm 0.0

Protocol

The protocol took 10 days. The first 4 days were baseline days, which the subjects spent at home. They were instructed to restrict sleep to midnight till 8 AM, to refrain from daytime naps, heavy physical exercise and alcoholic beverages. Furthermore, they were asked to drink not more than four caffeine containing drinks a day. Compliance to the sleep-wake schedule was verified by an actometer, which the subjects continuously wore at the non-dominant wrist (Bakker and Beersma 1991).

On day 4, subjects were admitted to the time isolation unit of the Psychiatry Department of the Groningen Academic Hospital. This facility comprises a sound and light shielded apartment in which no information on time of day is available. A habituation period from 6 PM on day 4 till 8 AM on day 5 enabled the subjects to become acquainted with the experimental procedures during wakefulness and sleep. Subsequently, the participants were subjected to a 120-h forced desynchrony protocol. Without knowledge of the timing of the experimental procedures, subjects were scheduled on six 20-h days consisting of 13.5 h of wakefulness in dim light (< 10 lux) and 6.5 h of darkness in which they had to be in bed. Staff members (conscious of revealing no information about time of day) had brief contacts with the subjects to announce the moments for rising, having meals, showering, performing psychometric tests, sticking electrodes for polysomnographic recordings and to announce the moments for going to bed. Therefore, each subjective 20-h day had the same temporal structure.

During time isolation, core body temperature and melatonin concentrations were assessed to study circadian pacemaker characteristics (period, phase, and amplitude). Core body temperature was measured continuously with a rectal probe and stored at 1-min intervals (Bakker and Beersma 1991). The endogenous circadian period was calculated from the salivary dim light melatonin onset (DLMO) obtained on days 4 and 9. On these days, saliva was sampled hourly between 7 PM and midnight and between 7 PM and 2 AM, respectively. To determine circadian phase and amplitude, the melatonin-derived value for circadian period was integrated into an iterative mathematical analysis of the temperature data (Hiddinga *et al.* 1997). In addition, every 2 h, starting 15 min after the scheduled wake-up time, subjects completed a psychometric test battery.

In between the scheduled activities during wakefulness, subjects could watch videos, listen to music or perform other leisure activities according to their own preference. In the subjective morning a maximum intake of four caffeine containing drinks was permitted. Subjects were continuously monitored by an infra-red camera.

Polysomnography

In time isolation, sleep was only allowed during seven intervals, the first of which was scheduled from 23.45 h on

day 4 until 08.15 h on day 5. This first period for sleep functioned as habituation period and was not included in further analyses. The other periods for sleep occurred during the forced desynchrony part of the study and were subsequently scheduled between 21.45 h (day 5)–04.15 h (day 6), 17.45 h (day 6)–00.15 h (day 7), 01.45 h (day 7)–20.15 h (day 7), 9.45 h (day 8)–16.15 h (day 8), 05.45 h (day 9)–12.15 h (day 9), and 01.45 h (day 10)–8.15 h (day 10). Each period for sleep in time isolation was evaluated by means of polysomnography (PSG), the preparations of which were scheduled 02.25 h before the start of the registration. Two EEGs, two electrooculograms (EOG) and one submental electromyogram (EMG) were continuously recorded (Rechtschaffen and Kales 1968). EEG signals were derived with reference to the contralateral mastoid process (C3–A2 and C4–A1). The EEG signals were low-pass filtered at 25 Hz (24 dB/oct). The time constant of the preamplifier was 1 s. EEGs were sampled at 128 Hz, and EOGs and EMGs at 64 Hz. Three raters visually scored the PSGs per 30-s epoch according to the criteria of Rechtschaffen and Kales (1968) assisted by VitaPort software (TEMEC Instruments, Kerkrade, Netherlands). Raters displayed an average agreement with assigned scores of 95.4% (range 94.1–96.3%), with an average largest disagreement interval of 3 min (range 1.5–4 min).

Sleep stage parameters

From each registration the following sleep stage parameters were computed: total sleep time (TST), SL, total minutes of NREM sleep during the recording (SNREM), total minutes of REM sleep during the recording (SREM), REM latency (REML), total minutes of stage 1 (S1), stage 2 (S2) and SWS (i.e. stages 3 and 4 combined) during the recording (SWS), and intermittent wakefulness (IW). TST was calculated by adding the minutes in sleep stages 1–4 and REM. SL was defined as the latency from lights-off to the first page of any sleep stage (stage 1 included). REML was obtained by computing the time asleep between sleep onset (first page of any sleep stage, including stage 1) and first page of REM sleep. Furthermore, the amount of SWS, NREM and REM expressed as a percentage of TST (SWS%; NREM%; REM%) were calculated. To compare the parameters between the various conditions regardless of possible pacemaker related influences, the data of all six periods for sleep scheduled during one forced desynchrony experiment were averaged per subject before comparing the conditions in which the subjects participated. Because the sleeping periods during the forced desynchrony experiment were scheduled across all circadian phases, the impact of the circadian pacemaker could thus practically be excluded.

The spectral composition of the NREM sleep EEG signal

Each 4-s epoch of all EEG signals was subjected to Fast Fourier Transformation (FFT) with a cosine-tapered window. Each subsequent epoch in the FFT analysis started 3 s later

than the previous one to account for the loss in power because of the tapering. The epoch duration of 4 s leads to a spectral resolution of 0.25 Hz. The frequencies included in the analysis ranged from 0.25 to 32 Hz. Except for one sleeping period containing 90 min of NREM sleep, all periods for sleep included at least 120 min of NREM sleep. Therefore, for each PSG recording during forced desynchrony, spectral power in each 0.25 Hz frequency bin was accumulated over the first 120 min of NREM sleep (i.e. the stages 1–4). For the one sleeping period of shorter duration, the results were proportionally corrected. For each subject, the power spectra obtained were normalized to the individual average power spectrum across all experiments. The six normalized spectra were averaged per condition to obtain the best estimate of the NREM power spectrum of the individual in that condition. Subsequently, the resulting individual mean power spectra were averaged per condition and the corresponding standard errors were calculated.

The time course of power in the various EEG frequency bands across the first three NREM–REM sleep cycles

A problem with studying the time course of EEG variables is the fact that individual recordings differ in the timing of the sleep stages. Changes in the spectral composition of the EEG signal around the transitions to and from REM sleep, for instance, can only be studied when those transitions are superimposed across nights. To study the time course of power in the various EEG frequency bands, the method described by Brunner *et al.* (1990) was used. The average duration of the first, second and third NREM and REM episodes were calculated for each sleeping period in forced desynchrony. A histogram plotting the number of NREM episodes as a function of their duration revealed a bimodal pattern with a clear trough at a duration of 30 min. NREM episodes shorter than 30 min in duration apparently are of a different nature as compared with NREM episodes longer than 30 min. Therefore those few (4.8%) NREM–REM cycles which incorporated a NREM episode shorter than 30 min were excluded from the analysis. Of 210 nights, 165 had three or more NREM–REM cycles. These nights were included in the analysis of the temporal course of power in the various frequency bands. In each condition, the missing data were replaced by the average values of the subjects who did complete three NREM–REM cycles in the sleeping period which occurred at that time of day. On average, the first NREM–REM cycles contained 62 min of NREM sleep and 23 min of REM sleep, the second cycle had 71 min of NREM sleep and 22 min of REM sleep and the third cycle had 65 and 22 min NREM and REM sleep, respectively. For each individual EEG recording, the various NREM and REM episodes were subsequently compressed or stretched in time to match the template defined by the average duration. This leads to synchronous transitions between NREM and REM sleep in all sleeping periods. The following frequency bands were studied: the delta band from 1.0 to 4.5 Hz; the theta band from 4.75 to 7.75 Hz; the alpha band

from 8.0 to 11.75 Hz, the sigma band from 12.0 to 14.75 Hz and the beta band from 15.0 to 19.75 Hz. As the relative power spectra are investigated separately, this analysis focuses on the time course of the signals. Therefore, for each night, the power in a certain frequency band on a certain moment was expressed relative to the average power in that band of the three NREM–REM cycles of that recording.

Statistical analysis

To reveal possible differences in sleep stage parameters between the various conditions in which SAD patients and controls participated, repeated measures ANOVAS were performed in which season was entered as the repeated measures factor and patient vs. control status as between subjects factor. In one ANOVA the patients in winter were studied in the depressed state, in the other ANOVA the patients' data of the remitted state were included in winter. Significance was accepted at $P < 0.05$. Differences between patients and controls and between conditions in the spectral composition of the sleep EEG were explored by means of sign tests. Power analyses were performed to estimate the smallest detectable differences between two groups or two conditions. This was achieved by calculating δ from the formula $n \geq 2(\sigma/\delta)^2 [t_{\alpha/2} + t_{2(1-P)/2}]^2$, with a power $P = 0.80$. In this formula n represents the number of replications, σ the true SD, δ = the smallest desired difference to detect, α the level of significance, P the intended power of the test, ν the degrees of freedom [$\nu = a(n - 1)$], a the number of populations, and $t_{0.05(12)} = 2.179$ and $t_{0.4(12)} = 0.873$ (Sokal and Rohlf 1981) (Table 2).

RESULTS

Sleep parameters averaged across circadian phase

For each condition, the average values for the various sleep parameters are listed in Table 2. Repeated measures ANOVAS did not reveal significant differences, neither between seasons nor between patients and controls (SL: $P = 0.413$; IW: $P = 0.671$; SWS: $P = 0.774$; SNREM: $P = 0.387$; SREM: $P = 0.364$; TST: $P = 0.736$; SWS%: $P = 0.724$; NREM%: $P = 0.248$; REM%: $P = 0.164$; REML: $P = 0.292$; S1: $P = 0.216$; S2: $P = 0.525$ and SWA: $P > 0.313$). The minimal detectable differences, given statistical power of 0.8, are indicated in Table 2. Patients exhibited shorter average REM latencies than controls in every condition. However, these differences were not significant. To test whether short REM latencies were more frequent in patients than in controls, the REM latencies obtained from each period for sleep in forced desynchrony were grouped in 10-min bins. The distribution of the binned REM latencies showed two peaks separated by a trough at the 30-min bin. Therefore, REM latencies were considered short when their duration was less than 30 min. Again, ANOVAS did not reveal significant differences in the prevalence of short REM latencies between patients and controls ($P > 0.209$), nor between seasons ($P = 0.079$).

Table 2 Mean values (\pm SEM) of sleep parameters of seasonal affective disorder (SAD) patients and healthy matched controls calculated from the six 6.5-h periods for sleep during the 120-h forced desynchrony protocol. The SAD patients participated during a depressive episode, remitted after light therapy and in summer. Controls participated once in winter and once in summer. Sleep latency (SL), is the latency from lights-off to sleep onset, i.e. the first page of any sleep stage (stage 1 included). REM latency (REML) is the time in any sleep stage between sleep onset and the first page of REM sleep. IW is intermittent wakefulness, S1 is total time in stage 1. S2 is total time in stage 2. Slow wave sleep (SWS), is the time in stage 3 and 4. SNREM is total time in NREM sleep. SREM is total time in REM sleep. Total sleep time (TST), is the total time in stages 1–4 and REM sleep. All parameters are expressed in minutes. SWS%, NREM% and REM% are the amounts of SWS, NREM sleep and REM sleep expressed as a percentage of TST. SWA is in μV^2 . Repeated measures ANOVAS with season as repeated measures factor and patient vs. control status as between subjects factor did not reveal significant differences. For each variable, the minimal detectable difference between two groups, given a power of 0.8, is called δ -min and provided in the last column

	SAD patients (<i>n</i> = 7)			Controls (<i>n</i> = 7)		δ -min
	Depressed	Remitted	Summer	Winter	Summer	
SL	10.0 \pm 0.9	8.5 \pm 1.4	9.1 \pm 1.5	9.6 \pm 1.0	10.1 \pm 1.2	5.2
REML	53.3 \pm 5.8	54.0 \pm 6.3	54.2 \pm 6.5	62.0 \pm 7.1	68.3 \pm 5.8	27.1
IW	41.5 \pm 11.7	36.6 \pm 12.4	34.1 \pm 10.6	28.1 \pm 8.4	36.4 \pm 11.0	46.5
S1	18.7 \pm 2.9	20.9 \pm 3.0	19.5 \pm 2.6	26.2 \pm 5.0	26.8 \pm 5.5	16.3
S2	135.6 \pm 11.6	144.7 \pm 10.3	147.2 \pm 9.2	146.5 \pm 8.7	143.7 \pm 8.5	41.5
SWS	88.0 \pm 14.8	86.6 \pm 12.8	86.6 \pm 13.0	87.7 \pm 7.9	89.5 \pm 8.7	49.1
SNREM	242.3 \pm 12.7	252.1 \pm 9.3	253.3 \pm 8.1	260.4 \pm 8.3	260.1 \pm 10.5	42.0
SREM	80.7 \pm 7.5	77.9 \pm 6.2	80.1 \pm 5.6	77.4 \pm 7.4	67.9 \pm 9.1	30.8
TST	324.1 \pm 18.6	330.7 \pm 13.8	334.2 \pm 11.7	339.4 \pm 10.7	331.1 \pm 15.4	60.3
SWS%	27.6 \pm 3.9	26.5 \pm 3.4	26.2 \pm 3.5	25.9 \pm 2.3	27.3 \pm 2.1	13.1
NREM%	75.6 \pm 1.6	76.5 \pm 1.2	76.1 \pm 1.1	77.0 \pm 1.8	79.3 \pm 2.5	7.0
REM%	24.1 \pm 1.5	23.3 \pm 1.2	23.7 \pm 1.2	22.6 \pm 1.7	19.9 \pm 2.0	6.5
SWA	994 \pm 199	888 \pm 173	866 \pm 157	1122 \pm 218	1124 \pm 197	811

The spectral composition of the NREM sleep EEG signal

For each condition, the log-transformed average power spectra of the first 120 min of NREM sleep are plotted in Fig. 1. Except for the 5.75–12.5 Hz frequency range (i.e. the theta–alpha band), the average power spectra are rather similar in the various groups and conditions. In the control group, comparison of the mean power spectra in winter with those obtained in summer revealed no significant differences. Therefore, the winter and summer spectra of controls were averaged. Plots of the mean power spectra of patients in the depressed, remitted and summer condition relative to the average control spectrum showed that in each condition patients manifested twice as much power than controls in the theta–alpha band. This was because of the contribution of two patients who consistently exhibited power densities in the theta–alpha band far above average. Therefore, the large interpatient differences are the reason that the differences observed in the average power spectra are not significant.

Time course of power in the various EEG frequency bands across the first three NREM–REM sleep cycles

Figure 2 depicts the time course of the power in (a) the delta band, (b) the theta band, (c) the alpha band, (d) the sigma band and (e) the beta band across the first three NREM–REM cycles for each condition. In each condition in which the subjects participated, the courses of the various frequency bands show a robust rhythmicity. Both delta or slow wave activity (SWA) and theta activity exhibit an increase at the start and a sharp decrease just before the end of each NREM

episode with an overall declining trend across the consecutive NREM–REM cycles (Fig. 2a,b). Similarly, the curves representing the alpha and sigma activity rise towards a peak value at the start of the NREM episode and gradually decline thereafter (Fig. 2c,d). Each time at the start of the REM episode, the amounts of alpha and sigma activity decrease even more and reach their lowest values at the end of the respective episode. Furthermore, in most of the NREM episodes, the alpha activity shows an initial decline before rising, whereas the sigma activity demonstrates a temporary increase at the end of the episode. Finally, the beta activity (Fig. 2e) exhibits a sharp diminution at the start of the NREM episode and a subsequent small rise towards the end of the episode. During the following REM episode, the beta activity drops again. Like the absolute power spectra, the curves representing the average time course of the various frequency bands appear to be similar in both groups. For each frequency band no systematic differences were found when the results of controls in winter were compared with those obtained in summer. Therefore, for each condition in which patients participated, the individual average course of each frequency band was expressed as a percentage of the winter–summer average of controls. Sign tests revealed no significant differences between patients and controls in almost all time bins. The only consistent difference observed is the slightly slower increase of delta power in the second NREM episode in the patients, in particular in winter. Of the total time of 109-min, there were two intervals of 4 min each within the second NREM episode in which relative SWA of depressed patients was less than controls. There was one interval of 6 min within the second NREM episode in which relative SWA of recovered patients was less than controls.

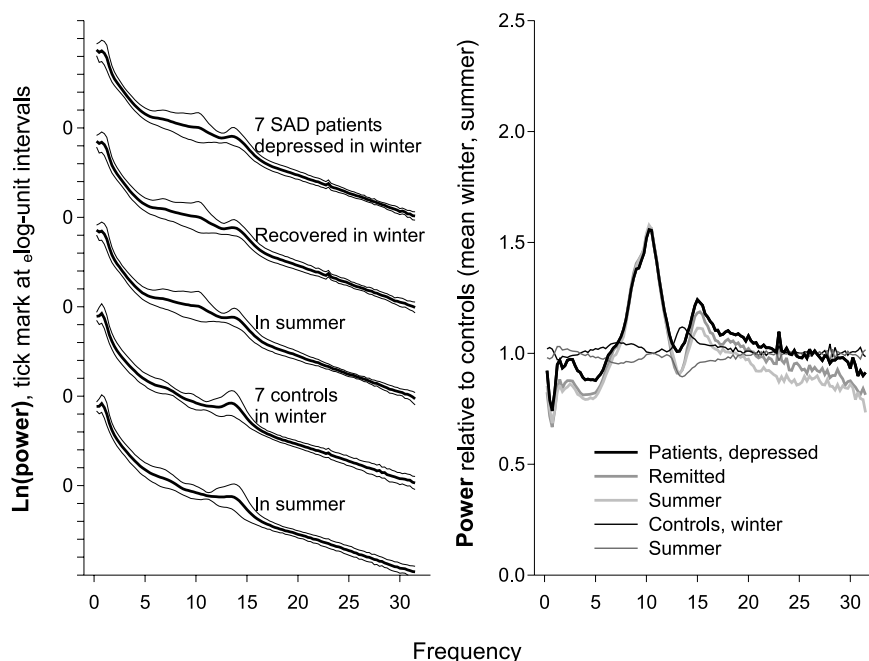


Figure 1. Power spectra (geometric mean \pm SEM) obtained in SAD patients and healthy matched controls subjected to a 120-h forced desynchrony experiment in which six 6.5-h periods for sleep scanned through all circadian phases. SAD patients participated during a depressive episode, remitted after light therapy and in summer. Controls participated once in winter and once in summer. For the first 120 min of non-rapid eye movement (NREM) sleep (stages 1–4 combined), the power in each 0.25 Hz frequency bin was calculated by means of Fast Fourier Transformation. For each subject, the six spectra were averaged per condition to obtain the best estimate of the NREM power spectrum in that condition. Subsequently, the geometric means of the resulting individual mean power spectra were calculated per condition and plotted on a logarithmic scale in the left panel (mean \pm SEM). The right panel shows the geometric mean power spectra per condition, plotted relative to the geometric mean of the summer and winter spectra of the controls.

There was one interval of 4 min within the second NREM episode in which relative SWA of patients in summer was less than controls. Obviously, these differences may be chance observations, given the large number of tests performed. Based on the standard deviations averaged over the 109 min interval, the minimal detectable differences between the groups for the various frequency bands are expressed as a fraction of the average power in each frequency band. They are 0.21 for the delta band, 0.19 for the theta band, 0.23 for the alpha band, 0.24 for the sigma band and 0.25 for the beta band.

DISCUSSION

Sleep is regulated by homeostatic, ultradian and circadian mechanisms. The present study focussed on the exploration of the homeostatic and ultradian aspects of sleep in SAD patients and healthy matched controls.

Although data were collected in a relatively small number of subjects, the design of the present study provides some major advantages over the previous studies of sleep in SAD. First, the study was designed in such a way that the influences of prior wakefulness and circadian phase could be minimized. Secondly, for each condition in which a subject participated, polysomnographic data were averaged across six recordings. Thereby, an accurate estimate of the individual's sleep characteristics was achieved. To the best of our knowledge, this is

the first time in which sleep of SAD patients was studied in a forced desynchrony protocol.

Like the majority of SAD patients (Anderson *et al.* 1994; Rosenthal *et al.* 1984), six of seven patients in the present study reported to be hypersomnic during their depressive episode. Nevertheless, the comparisons between the various conditions in which patients and controls were studied did not reveal abnormalities in the sleep stage parameters, the power spectra and time course of power in various frequency bands across the first three NREM–REM cycles. Similar to the finding of Brunner *et al.* (1996), the results of the present study suggest that in SAD the regulation of sleep is not affected. This absence of polysomnographically recorded sleep abnormalities is in contrast with the findings in most previous studies of sleep in SAD (Anderson *et al.* 1994; Endo 1993; Endo *et al.* 1992; Kohsaka *et al.* 1994; Palchikov *et al.* 1997; Rosenthal *et al.* 1984, 1985, 1989; Schwartz *et al.* 2000). However, these studies have not provided a consistent picture of sleep in SAD. The most likely reason for the inconsistencies is that the studies varied with respect to factors known to influence sleep regulation. These factors included restriction of sleep duration, circadian timing of sleep and composition of the subject groups with respect to age, gender and menstrual cycle phase (Daan *et al.* 1984; Dijk and Czeisler 1995; Dijk *et al.* 1989, 1999; Driver *et al.* 1996). Therefore, in the present study patients and healthy controls were instructed to adhere to the

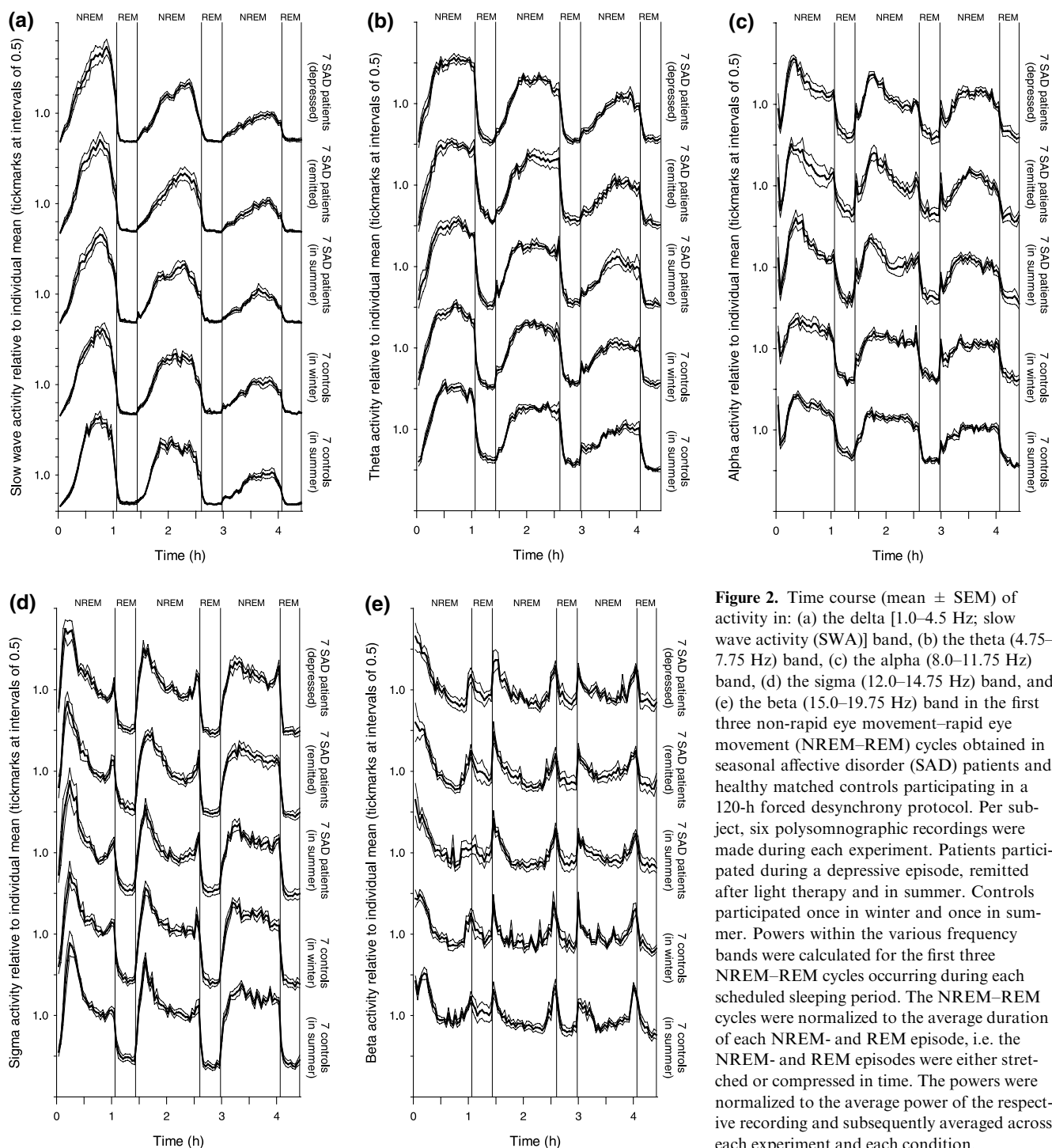


Figure 2. Time course (mean \pm SEM) of activity in: (a) the delta [1.0–4.5 Hz; slow wave activity (SWA)] band, (b) the theta (4.75–7.75 Hz) band, (c) the alpha (8.0–11.75 Hz) band, (d) the sigma (12.0–14.75 Hz) band, and (e) the beta (15.0–19.75 Hz) band in the first three non-rapid eye movement–rapid eye movement (NREM–REM) cycles obtained in seasonal affective disorder (SAD) patients and healthy matched controls participating in a 120-h forced desynchrony protocol. Per subject, six polysomnographic recordings were made during each experiment. Patients participated during a depressive episode, remitted after light therapy and in summer. Controls participated once in winter and once in summer. Powers within the various frequency bands were calculated for the first three NREM–REM cycles occurring during each scheduled sleeping period. The NREM–REM cycles were normalized to the average duration of each NREM- and REM episode, i.e. the NREM- and REM episodes were either stretched or compressed in time. The powers were normalized to the average power of the respective recording and subsequently averaged across each experiment and each condition.

same sleep schedule in the days prior to the study. Patients and controls were matched for age and sex. Moreover, the premenopausal female subjects were matched for the menstrual cycle phase and were studied in the same phase of their menstrual cycle, if possible. Only two of the previous studies of sleep in SAD patients and controls compared groups that were matched for the majority of these characteristics (Brunner *et al.* 1996; Schwartz *et al.* 2000, 2001). In a sample of 23 patients and controls, Schwartz *et al.* (2001) reported higher

power densities in the delta–theta–alpha bands of the EEG, both in NREM sleep and REM sleep, the differences being only significant in NREM sleep. In our study, repeated measures ANOVAS did not reveal significant effects of season nor of patient vs. control status. In support of Schwartz *et al.* (2001), we noted that SWA values are significantly higher in the patients when depressed as compared with the patients when recovered in winter. Yet, average values of SWA are lower in the patients than in the controls, not higher. The

discrepancy between our study and Schwartz *et al.* (2001) may well be because of our small sample size. Yet, the fact that in Schwartz *et al.*'s (2001) study, the differences between patients and controls observed in REM sleep are similar in size (though not statistically significant) as the differences in NREM sleep raise some doubts as to whether those differences can be interpreted to demonstrate differences in homeostatic sleep control.

A major concern of the present study is the small number of subjects studied and the large number of tests performed. Patients and controls have to differ very systematically before significant results can be obtained. The negative results therefore have to be taken with care. The study is just exploratory in nature. This also applies to the statistical testing. We have compared each minute of sleep in five frequency bands between the groups and conditions. It is obvious that among those hundreds of comparisons some will be significant even if random fluctuations were the only source of variation. The few minutes in which a difference between conditions was observed are less than the 5% expected. This could be because of the fact that successive minutes of EEG are not completely independent. The present study can do no more than indicate that there may be a difference between patients and controls in the rate at which SWA accumulates in the second NREM episode. Additional hypothesis driven research is required to substantiate this observation.

The data regarding the time course of the various EEG frequency bands during the first three NREM-REM cycles are in accordance with data obtained in studies of polysomnographically recorded sleep in healthy subjects. The SWA recorded under baseline conditions has been found to decline during sleep (Achermann *et al.* 1993; Brunner *et al.* 1990; Schwartz *et al.* 2000; Werth *et al.* 1997). Similarly, in forced desynchrony studies SWA has been found to show a sleep-dependent decrease (Dijk and Czeisler 1995; Wyatt *et al.* 1999).

The present study focussed on sleep homeostasis, as derived from the dynamics of the power in certain EEG frequency bands during sleep. Globally, sleep homeostasis consists of two aspects. Apart from a decrease in sleep need during sleep, there is also an increase in sleep need during wakefulness. Commonly, sleep homeostasis is thought to be monitored by SWA during NREM sleep. Several studies recently proposed measures related to sleep homeostasis that can be obtained during wakefulness, like slow eye movements (Cajochen *et al.* 2000b) and theta and alpha power in the wake EEG (Aeschbach *et al.* 2001). In the lack of such wake-related data, the present study cannot conclude anything about the waking component of sleep homeostasis.

To conclude, the present study of homeostatic and ultradian aspects of sleep did not reveal differences between SAD patients and controls. Therefore, the results do not support the hypotheses concerning the involvement of process S in the pathogenesis of (seasonal) affective disorder.

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